NIDDK Generic Data And Safety Monitoring Plan

For Clinical Trials *Requiring*

A Data And Safety Monitoring Board (DSMB)

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INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), has identified the need to assist grantees conducting clinical trials by providing generic monitoring plans. Ongoing study monitoring of treatment outcomes is recognized as the ethical responsibility of study investigators to their participants (Friedman *et al*, 1996; Meinert, 1986; Weiss, 1996).

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subjects research projects and to protect the safety of human subjects. Meinert (1986) defines safety monitoring as any process during a clinical trial that involves the review of accumulated outcome data for groups of patients to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998) specify that all clinical trials should have in place a system for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities should be commensurate with the nature, size, and complexity of the trial. For a small, single center study, a statistician in conjunction with a Safety Officer usually performs the monitoring. However, for single site, high-risk trials, a monitoring committee called a Data and Safety Monitoring Board (DSMB) may be in order. For larger, single or multi-center, clinical trials, monitoring is usually performed by a DSMB. Ongoing review of the data by an independent individual or committee assures the investigators that the trial can continue without jeopardizing patient safety.

Data monitoring during an ongoing study focuses on several areas:

- ***Performance*** - to assess sites' performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data;
- ***Safety*** - to assess the magnitude of adverse events; and
- ***Treatment*** - to monitor and assess treatment effects.

In multi-center studies, ***performance monitoring*** should be an ongoing activity performed by the study investigator and statistician, and reviewed by the DSMB. Performance data are reviewed in a blinded fashion, often in aggregate by site, and thus do not raise unblinding or bias issues. The investigator and statistician also perform ongoing safety review of the data, and safety reports are reviewed at regularly scheduled DSMB meetings. In some studies where the treatment may be toxic or potentially result in severe adverse events, the protocol may specify an unblinded safety review by the study statistician or an independent clinician. ***Treatment monitoring or interim analyses*** by the statistician are formal processes that are specified in the protocol or by the DSMB. An interim analysis can result in early study termination if continuation will not produce benefit to patients or if the treatment outcome is known to have benefit. Meinert (1986) points out that ethical questions arise if studies continue beyond where the outcome is known and cites the Tuskegee Syphilis Study as an example. In this study, patients with syphilis were allowed to continue in the study for years even though it was known that

the treatment under study, penicillin, was beneficial. ***Stopping rules***, developed and implemented early in a study, specify the conditions under which a study may be stopped.

NIDDK recognizes that setting up the procedures for study monitoring and for developing reports for the DSMB can be a daunting task for investigators embarking on their first multi-center study. This Guide provides a general approach to developing monitoring plans and incorporates the following:

- ***A list of issues*** to consider when developing a study safety monitoring plan that can form a checklist;
- ***A discussion of statistical issues and stopping rules*** along with examples and references; and
- ***An outline of DSMB data reports*** along with sample data presentations, their rationale and general data elements to be included.

CONSIDERATIONS IN DESIGNING A SAFETY MONITORING PLAN

There is no simple formula for how often data should be reviewed or how frequently relevant parties should meet. These decisions are usually set out in the protocol by the study statistician and are reviewed by the DSMB, who may develop a set of bylaws that govern these activities. To assist the study team and the DSMB in formulating the safety-monitoring plan, the following considerations should be reviewed.

Study Phase

Phase I, II and III studies generally require different levels of safety monitoring scrutiny. For many phase I and phase II trials, an independent DSMB may not be necessary or appropriate when the intervention is low risk or because of their small size and short duration. Instead, continuous, close monitoring by the study investigator in conjunction with a Safety Officer may be an adequate and appropriate format for monitoring, with prompt reporting of toxicity to the IRB, FDA and/or NIH. In situations involving potentially high risks or special populations, investigators must consider additional monitoring safeguards. For example, for studies involving children, investigators may consider the use of a consent monitor to ensure that informed consent or assent is properly administered. In addition, those trials with high risk (gene transfer, stem cell, etc.) will require a DSMB.

As studies progress through Phase II and III, a DSMB is required. As the intensity and frequency of safety monitoring increases and as the number of subjects and sites increase, dosing levels are tested, and subjects are randomized to interventions. The need to document the safety profile of the drug, or likely adverse events, and to insure data integrity requires more frequent and more rigorous views of the data.

Regulatory Considerations

There are additional administrative considerations if the clinical trial requires compliance with FDA regulations. Monitoring should conform to Good Clinical Practice (GCP) and International Committee on Harmonization (ICH) guidelines. Study phase (I-III) and plans for Investigational New Drug Application (IND) submission also influence the frequency and intensity of monitoring studies. Pivotal studies that will influence the outcome of an IND are generally subjected to rigorous monitoring. While it is often argued that the safety profile of a drug is known by the time a Phase III is conducted, early studies are generally conducted in small populations. Thus, adverse events may remain undetected. Further, other safety concerns such as futility of outcome, protocol adherence, site performance, and data quality need careful scrutiny.

Trial Design

The design of the trial is, in part, related to the study phase. As studies move from Phase I through Phases II and III, more subjects are required, and again, greater variability in both study implementation and subject population may occur. In addition, adverse events are more likely to emerge as more people are exposed to the intervention. In multi-center clinical trials, there is greater need to examine site-specific data collection and outcomes and inter-site differences.

Later Phase II and all Phase III studies are generally designed as randomized, controlled, clinical trials. Because the subject and investigator are blinded it cannot be determined if the adverse events that occur are related to the drug. Thus, careful review of the data both aggregate and by treatment group in a blinded fashion should take place at regularly scheduled intervals. If adverse events occur in different proportions in the study groups and there are concerns regarding the negative effects of the intervention, then the study statistician, and/or the DSMB may decide to unblind themselves to protect the safety of the study subjects.

Disease/Syndrome under Investigation

The nature of the disease being studied may influence the safety-monitoring plan. When the natural history of a disease is known, the investigators and the DSMB are more likely to anticipate the nature and frequency of adverse events. However, investigators must consider additional monitoring safeguards when vulnerable populations and/or high-risk diseases are involved. For example, studies involving the elderly or pediatric populations may require more extensive and detailed monitoring. A DSMB will be required for those studies involving high risk such as gene therapy or stem cells.

A monitoring plan should consider the nature of the intervention. The level of scrutiny will depend on the severity of the disease and may require frequently scheduled safety reviews. The same approach may be needed if the disease is serious and/or life threatening and endpoints are anticipated to occur frequently and/or early in the study.

Study Population

The nature of the disease and the trial design will influence the size and characteristics of the subject population. Phase I and II studies have smaller subject populations and treatment studies for diseases are likely to include subjects of similar demographic and health statuses. Phase III studies have larger subject populations. Treatment studies for diseases such as hepatitis and diabetes are likely to include subjects of different demographic and health backgrounds.

The diversity of a study population can be controlled, to some degree, by the inclusion/exclusion criteria which determine who is eligible to participate in a study. In some studies, eligibility criteria will increase the homogeneity of the patient population. Increased homogeneity may decrease the number of confounding variables that will be considered during analysis. However, stringent inclusion/exclusion criteria may also hinder subject recruitment and accrual to the study. It is therefore important to strike a balance between these two competing demands so that subjects can be recruited to a study in a timely and cost effective manner and that the study yields results that are of high quality and confirm the efficacy of the intervention. This consideration protects the subject's safety in that he/she is not committed to a study that is unduly extended over time or that shows no hope of successfully evaluating the intervention.

The safety plan should specify a review of the rate of subject accrual by site and by the study overall, the sites' adherence to inclusion/exclusion criteria and other protocol requirements, and the expected compliance rate of the subjects. Studies in which the study requirements are invasive, the intervention causes many adverse events, or the target population is very old, very young, or marginal (e.g., homeless, mentally ill, etc.) may have difficulty accruing and retaining subjects. Careful monitoring of the recruitment, enrollment and retention activities will help to protect the safety of study subjects, integrity of the study and the quality of the data.

If subject accrual is expected to occur quickly, then safety monitoring should take place early and may be tied to a percent of the total population to be accrued. For example, if 60 subjects are to be recruited in six months, safety review can take place after the first month of enrollment or after the first 10% of the subjects are enrolled, whichever comes first.

Study Intervention

The more that is known about the study treatment, the easier it is to plan for the monitoring of the study. As discussed, treatments that have been studied previously are more likely to have a known safety profile and the frequency and type of adverse events can be anticipated. However, the safety of a treatment is also related to the population being treated, the indication for its use, dosing level and frequency, the presence of co morbid diseases, and the subject's time on study drug. All of these factors need to be considered in deciding on the frequency and intensity of safety monitoring as well as the types of reports, e.g., number of adverse events per subject.

Endpoints/Outcome Variables

Endpoints that are well defined and immediate are easier to monitor. Acute illnesses are more likely to have these types of outcomes. For example, treatment of an acute infection with the study drug is likely to yield clear-cut results in a relatively short period of time.

In contrast, outcomes from chronic illnesses such as diabetes and heart disease may require a longer treatment intervention and follow-up period. Thus, the subject's time on study intervention and in the study from baseline through final follow-up will influence the type and frequency of safety monitoring.

DESIGNING THE SAFETY MONITORING PLAN

Once the study design and population are specified, the clinical investigators can design, with the study statistician, the study safety monitoring plan. The monitoring plan should specify the responsibilities of the DSMB, including frequency of data review, triggers for ad hoc reviews, and contents and format of the safety reports. In addition, specific instructions as to whom each report will be sent (e.g., DSMB, NIDDK, FDA), and what procedures, if any, the PI or recipient(s) should follow (e.g., DSMB will forward the report void of patient-specific information to the IRB, NIDDK) to ensure that pertinent parties receive these documents.

Review Process

The monitoring plan should delineate the review process and the roles of the Data Coordinating Center (DCC), the study statistician, and the DSMB in relation to the content, format, and process of the review. Typically, the DCC produces administrative reports that describe study progress including accrual by site, demographics in aggregate and by site, as well as subjects' status in aggregate and by site. Reports might describe outstanding study forms or error rates by site and in aggregate regarding adherence to inclusion/exclusion criteria and the study protocol. These reports are reviewed internally by the DCC for ongoing quality control and are also presented to the DSMB and NIDDK.

Safety Reports

The DCC also produces safety reports that list adverse events, serious adverse events, deaths, and disease or treatment specific events by site and in aggregate for DSMB meetings. In some studies of treatments with an unexpected high toxicity, an independent medical monitor may review each adverse event or treatment description to ensure good clinical care and to quickly identify any potential trends. In other studies, the statistician may review data routinely and will alert NIDDK and the DSMB if event rates are of statistical concern, occur in a disproportionate number in one of the treatment groups, or fall out of a pre-determined set of boundaries. The study statistician may distribute interim reports to the DSMB between meetings to allow members to call special sessions when appropriate. In some studies, the Statistical Coordinating Center (SCS) is separate from the DCC. In these cases, the DCC may prepare reports for the SCC or may send the SCC the data. ***The review plan should specify the process for reporting safety concerns among the medical monitor, the IRB, DSMB, NIDDK and, if appropriate, the FDA.***

Typically, the DSMB reviews the safety reports in aggregate fashion and by blinded treatment group. If there are a significant number of adverse events, the DSMB may request that the treatment groups be unblinded to ensure that there are not untoward treatment effects. ***The review plan should specify how data are to be presented and triggers for presenting safety data in an unblinded manner.***

Interim Analysis

The DCC also prepares the data for the study statistician to analyze in conformance with an interim analysis. The coordinator must have procedures in place for preparing the data for the analyses and for "freezing" the data set so that additional analyses may be performed or the analyses recreated, if necessary. The schedule for interim analyses can be a fixed time frame (e.g., every six months), after a certain number or percentage of subjects are enrolled (e.g., 25%, 50%, 75%, 100%), or in response to a specific number of occurrences of an event (e.g., *n* deaths).

Independence of Review

The DSMB should be separate and independent from the clinical staff or anyone responsible for patient care. Members of the DSMB should not have scientific, financial, or other conflict of interest related to the trial. Current collaborators or associates of the PI (i.e., same institution) are not eligible. Clinicians should be blinded to the safety monitoring data, as exposure to emerging trends may influence enrollment and care, thus biasing the study.

Steps Emanating from Review

Statistical considerations, such as alpha spending and early stopping are discussed below in the section on statistical issues. The review may result in an amendment to the protocol, which must be approved by the IRB, NIDDK, DSMB, and FDA (if appropriate). If the review causes changes to the data collection plan or study forms, then there should be a set of procedures for documenting and implementing these changes since the study data sets and analyses may also be affected. The monitoring plan should also specify what steps will be taken as a result of the review and should consider the impact of the review on the study.

STATISTICAL CONSIDERATIONS

Statistical issues arise with ongoing data monitoring such as the "multiple testing" problem, spending the study "alpha", and powering the study for "multiple looks". These issues and associated methods are addressed in the monitoring plan and are briefly discussed. References provide more robust discussion of these issues.

"Multiple looks" at the data during interim analyses can reduce the power of a study. Thus, there is an inverse relationship between the number of interim analyses and the interim p-values for significance. Pocock (1977) recommends that the significance levels for all interim analyses be the same. For example, assuming five interim analyses, a significance level of 1.6% achieves an overall 5% significance. O'Brien and Fleming (1979) modify this rule so that the significance levels begin lower and end at the final analysis closer to the desired overall significance level. The adjustment of the analytic plan and significance level(s) for interim analysis is referred to as the 'alpha spending' function. The 'boundary conditions' described by the interim and final significance levels are symmetrically 2-sided if it is important to measure both the potential positive and negative effects of a treatment vis-à-vis the placebo.

STOPPING RULES

A 'stopping rule' specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial. The stopping rules reflect one of the following conditions:

- There is clear evidence of harm or harmful side-effects of the treatment;
- There is no likelihood of demonstrating treatment benefit; or
- There is overwhelming evidence of the benefit of the treatment.

One of the benefits of stopping rules is that they can prevent over-reaction to random highs or lows in treatment response rates and adverse events since they generally require very low threshold p-values in interim analyses to indicate significance.
However, stopping rules, also called 'discontinuation guidelines,' are not sufficient to justify stopping a trial for several reasons:

- ***New Information*** **-** There may be new information available such as the results of other trials, a change in the understanding of the underlying biology or outside evidence of unacceptable adverse effects.
- ***Limits of Assumptions*** **-** Assumptions in the trial design regarding sample size and power, subject recruitment, the adverse event profile, and anticipated treatment affect differences may prove to be false when the trial is underway.
- ***Limits of Rules*** **-** Rules cannot be developed for all potential study scenarios and contingencies.

Stopping a trial early, even if justified, has consequences. The scientific purpose behind clinical trials is to calculate with some assurance the size of the differences between treatment outcomes. With less than a full complement of events recorded, the confidence intervals associated with estimates of treatment effects are larger. Another consequence of early stopping is to bias the estimates of treatment effect upward. This bias occurs because random high values in treatment effect may be used to justify early stopping, but rarely would random low values be so used.

Stopping rules should be defined in the statistical plan or early in a study and require realistic estimates of sample size to be effective. Optimistic subject accrual projections often mean that the trial is unable to show the test effect with the necessary assurance. Stopping rules are no more reliable than the data on which they are based. Thus, the quality of the data must be ascertained for the interim analyses.

Before employing stopping rules, there are a host of issues that should be considered, according to Friedman (1996):

- ***Group Differences*** - Possible differences in baseline characteristics and prognostic factors between the two groups should be explored and necessary adjustments made in the analysis.

- ***Response Variables -*** Potential bias in the assessment of response variables must be considered, especially when the trial is not double-blinded.

- ***Missing Data -*** Possible impact of missing data should be evaluated. For example, could the conclusions be reversed if the experience of participants with missing data form one group were different from the experience with missing data from the other group?

- ***Protocol Compliance -*** Different participant protocol compliance should be evaluated for possible impact.

- ***Side Effects -*** Potential side effects and outcomes of secondary response variables should be considered in addition to the outcome of the primary response variable.

- ***Subgroup Consistency -*** Internal consistency across subgroups and various outcome measures should be examined.

Relevant statistical methods used in monitoring include classical or group sequential methods, flexible group sequential procedures, applications of group sequential boundaries, asymmetric boundaries, curtailed sampling procedures, and other approaches. These methods are discussed in numerous statistical methods books for clinical trials, a few of which are included in the bibliography.

OUTLINE OF TYPICAL DSMB REPORT

Attachment A contains an outline for a typical DSMB Report that is prepared by the study's Data Management or Statistical Coordinating Center, depending upon the structure and nomenclature of a specific study. The report begins with a brief narrative section that describes the status of the study, progress or findings to-date, issues, and the procedures that produced the report (e.g., data obtained by a specific date). The report provides a study description along with a current organization chart, current timetable and study schedule as well as a list of study clinical and administrative centers.

Data are then presented that describe the administrative status of the study including recruitment and forms handling. Study data reports describe demographic and baseline clinical characteristics and provide a safety assessment. These tables are generally provided by site as well as for the whole study population. The intent of the tables in this section is to provide a general scope of a typical DSMB report. The specifics of the study (i.e., the patient population, severity of the disease, and treatment) will guide the requirement for any tables necessary for routine DSMB reports and interim analyses.

After receipt and review of the Safety Report, the DSMB sends a brief evaluation highlighting any concerns, with recommendations as to whether or not the trial will continue, to the NIDDK and to the PI. It is the responsibility of the PI to forward this report to the IRB as well as to the other investigators in the study. Those investigators are then responsible for sending the evaluation to their own IRB.

REFERENCES

Armstrong PW; Furberg CD. Clinical Trial Data and Safety Monitoring Boards. The Search for a Constitution [editorial]. *Circulation* 1995(Feb1); 91(3): 901-4.

Ashby D; Machin D. Stopping Rules, Interim Analysis and Data Monitoring Committees [editorial]. *Br J Cancer* 1993(Dec);68(6):1047-50.

Bauer P; Kohne K. Evaluation of Experiments with Adaptive Interim Analysis. *Biometrics* 1994(Dec);50(4):1029-41.

Baum M; Houghton J; Abrams K. Early Stopping Rules-Clinical Perspectives and Ethical Considerations. *Stat Med* 1994(July 15-30);13(13-14):1459-69; discussion 1471-2.
Berntsen RF; Rasmussen K; Bjornstad JF. Monitoring a Randomized Clinical Trial for Futility: the North-Norwegian Lidocaine Intervention Trial. *Stat Med* 1991(Mar);10(3):405-12.

Burke G. Discussion of 'Early Stopping Rules-Clinical Perspectives and Ethical Considerations'. *Statistics in Medicine* 1994;13:1471-1472.

Buyse M.. Interim Analysis, Stopping Rules and Data Monitoring in Clinical Trials in Europe. *Stat Med* 1993(Mar);12(5-6):509-20.

Christiansen DH; Sundin D. A Data Model for Clinical Study Status Reports. *Drug Information Journal* 1998;32:887-895.

Chuang-Stein C. Safety Analysis in Controlled Clinical Trials. *Drug Information Journal* 1998;32:1363S-1372S.

Chow, Shein-Chug. Good Statistics Practice in the Drug Development and Regulatory Approval Process. *Drug Information Journal* 1997;31:1157-1166.

Cullen DJ; Bates DW; Small SD; Cooper JB; Nemeskal AR; Leape LL. The Incident Reporting System does not Detect Adverse Drug Events: a Problem for Quality Improvement. *Jt Comm J Qual Improv* 1995(Oct);21(10):541-548.

DeMets DL; Fleming TR; Whitley RJ; Childress JF; Ellenberg SS; Foulkes M; Mayer KH;O'Fallon J; Pollard RB; Rahal JJ; Sande M; Straus S; Walters L; Whitley-Williams P. The Data and Safety Monitoring Board and Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials. *Controlled Clinical Trials* 1995;16:408-421.

Dutar C; Otun EO. A Worldwide Strategy for Dictionary Management. *Drug Information Journal* 1996;30:137-142.

Ellenberg SS; Myers MW; Blackwelder WC; Hoth DF. The Use of External Monitoring Committees in Clinical Trials of the National Institute of Allergy and Infectious Diseases. *Statistics in Medicine* 1993(Mar);12(5-6):461-467; discussion 469.

Ellenberg SS. The Use of Data Monitoring Committees in Clinical Trials. *Drug Information Journal* 1999;30:553-557.

Fairweather WR. Integrated Safety Analysis: Statistical Issues in the Assessment of Safety in Clinical Trials. *Drug Information Journal* 1996;30:875-879.

Freidlin B; Korn EL; George SL. Data Monitoring Committees and Interim Monitoring Guidelines. *Controlled Clinical Trials* 1999;20:395-407.

Friedman LM; Furberg CD; DeMets DL. *Fundamentals of Clinical Trials.* Mosby-Year Book, Inc.: 1996.

Heitjan DF; Houts PS; Harvey HA. A Decision-Theoretic Evaluation of Early Stopping Rules. *Stat Med* 1992(Mar);11(5):673-83.

Hughes MD; Freedman LS; Pocock SJ. The Impact of Stopping Rules on Heterogeneity of Results in Overviews of Clinical Trials. *Biometrics* 1992(Mar);48(1):41-53.

Kim K; Tsiatis AA. Study Duration for Clinical Trials with Survival Response and Early Stopping Rule. *Biometrics* 1990(Mar);46(1):81-92.

McPherson K. Sequential Stopping Rules in Clinical Trials. *Stat Med* 1990(Jun);9(6):595-600.

Meinert CL. *Clinical Trials: Design, Conduct, and Analysis.* Oxford University Press, New York: 1986.

National Institutes of Health (1998, June 10). NIH Policy for Data Safety Monitoring [Online]. Available HTTP: Http://www.nih.gov/grants/guide/notice-files/not98-084.html

National Institutes of Health (2000, June 5) Further Guidance on Data and Safety Monitoring for Phase I and Phase II trials [Online}. Available HTTP: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

National Institutes of Health (2001, August 8) NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research [Online]. Available HTTP: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html

O'Brien PC; Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-556.

Pignon JP; Arriagada R. Early Stopping Rules and Long-term Follow-up in Phase III Trials. *Lung Cancer* 1994(Mar);10 Suppl 1:S151-9.

Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977;64:191-199.

Pong A; Shein-Chung C. Statistical/Practical Issues in Clinical Trials. *Drug Information Journal* 1997;31:1167-1174.

Routledge PA; Biala MC; Houghton JE; Woods F. Adverse Drug Reactions: The Great Masqueraders. *Drug Information Journal* 1998;32:79-84

.

Sankoh AJ. Interim Analyses: An Update of an FDA Reviewer's Experience and Perspective. *Drug Information Journal* 1999;33:165-176.

Shein-Chung C. Good Statistics Practice in the Drug Development and Regulatory Approval Process. *Drug Information Journal* 1997; 31:1157-1166.

Singer, DE. Problems with Stopping Rules in the Trials of Risky Therapies: the Case of Warfarin to Prevent Stroke in Atrial Fibrillation. *Clin Res* 1993(Oct);41(3):482-6.

Souhami, Robert L. The Clinical Importance of Early Stopping of Randomized Trials in Cancer Treatments. *Statistics in Medicine* 1994;13:1293-1295.

Schwarz, PJ. How Reliable are Clinical Trials? The Importance of the Criteria for Early Termination. *Eur Heart J* 1995(Aug);16 Suppl G:37-45.

Thall PF; Simon RM; Estey EH. Bayesian Sequential Monitoring Designs for Single-Arm Clinical Trials with Multiple Outcomes. *Statistics in Medicine* 1995;14:357-379.

Wallander MA; Lundborg P; Svardsudd K. Adverse event monitoring in clinical trials of felodipine and omeprozole. *Eur J Clin Pharmacol* 1992;42(5):517-522.

Weiss NS. *Clinical Epidemiology: The Study of Outcome of Illness*. Oxford University Press; New York: 1996.

Winkler G; Marsh R. Creating a Successful CRO-Sponsor Relationship Through Alignment of Goals and Values. *Drug Information Journal* 1996;30:113-117.

Wittes J. Behind Closed Doors: The Data Monitoring Board in Randomized Clinical Trials. *Statistics in Medicine* 1993;12:419-424.

Zidek W; Spiecker C; Knaup G; Steindl L; Breuer HW. Comparison of the Efficacy and Safety of Nifedipine Coat-Core Versus Amlodipine in the Treatment of Patients with Mild-to-Moderate Essential Hypertension. Hypertension Study Group. *Clin Ther* 1995(Jul-Aug);17(4):686-700.

APPENDIX A:

Sample Reports for Studies Requiring a DSMB

Table of Contents

Introduction

In general your monitoring plan should include a statement as to who your DSMB members are (if approved by NIDDK prior to the writing of the plan) or what type of credentials your intended DSMB members will possess. The plan should list all information to be included in reports, with copies of the reports intended, and at what intervals throughout the trial the DSMB receive trial updates. In addition, specific instructions as to whom each report will be sent [e.g., DSMB, NIDDK, FDA], and what procedures, if any, the PI or recipient(s) should follow (e.g., DSMB will forward the report void of patient-specific information to NIDDK) to ensure that pertinent parties receive these documents. Procedures should also be in place for assuring that a copy of the DSMB recommendation for continuation of the study is forwarded to the IRB (e.g. PI will forward to all investigators and to all IRBs involved in the study).

DSMB Report Outline

The actual structure and content of the DSMB report will have to be adjusted to the type of study that is being performed. The following is an outline of the type of report the DSMB should receive:

I. Table of Contents

II. Narrative/Trial Summary

A. Summary of Main Findings
B. Discussion of Issues or Problems
C. Report Preparation Procedures

III. Study Description

A. Project Organizational Chart, Personnel
B. Brief Statement of Purpose of Trial
C. Projected Timetable and Schedule
D. List of Participating Clinics, Data Centers, Resource Centers

IV. Study Administration

A. Recruitment and Subject Status

- Table 1: Site Enrollment by Year or Month of Study
- Figure 1: Comparison of Target to Actual Enrollment by Month
- Figure 2: Comparison of Target to Actual Enrollment by Site
- Table 2: Overall Subject Status by Site
- Table 3: Subject Status-Detail by Site

B. Forms Status

- Table 4: Data Flow to Coordinating Center By Visit and Site
- Table 5: Status of Forms at Coordinating Center

V. Study Data Reports (including Interim Analysis)

A. Recruitment and Subject Status

- Table 6: Race/Ethnic Characteristics for All Subjects
- Table 7: Race/Ethnic Characteristics by Site
- Table 8: Demographic and Key Baseline Characteristics by Group

B. Safety Assessment For All Subjects
[may also be recorded by Blinded Treatment Group (closed session)]

- Table 9: Treatment Duration for All Subjects
- Table 10: Treatment Duration for Subjects Who Discontinue Therapy
- Table 11: Adverse Events by Site and Subject
- Table 12: Serious Adverse Events by Site and Subject
- Table 13: Deaths by Site
- Table 14: Frequency of Specific Symptoms
- Table 15: Observed Adverse Events by Body System
- Table 16: Laboratory Data By Patient (Relevant Labs) Out of Range Values
- Table 17: Subject Status by Site and Group
- Figure 3: Average Cumulative Dose by Group

Table 1. SITE ENROLLMENT BY YEAR OR MONTH OF STUDY

Date: _____

Site Number and Name	First Patient Enrolled	Last Patient Enrolled	2000	2001	Total(%)
1					
2					
3					
4					
N					
Total					

Figure 1. COMPARISON OF TARGET TO ACTUAL ENROLLMENT BY MONTH

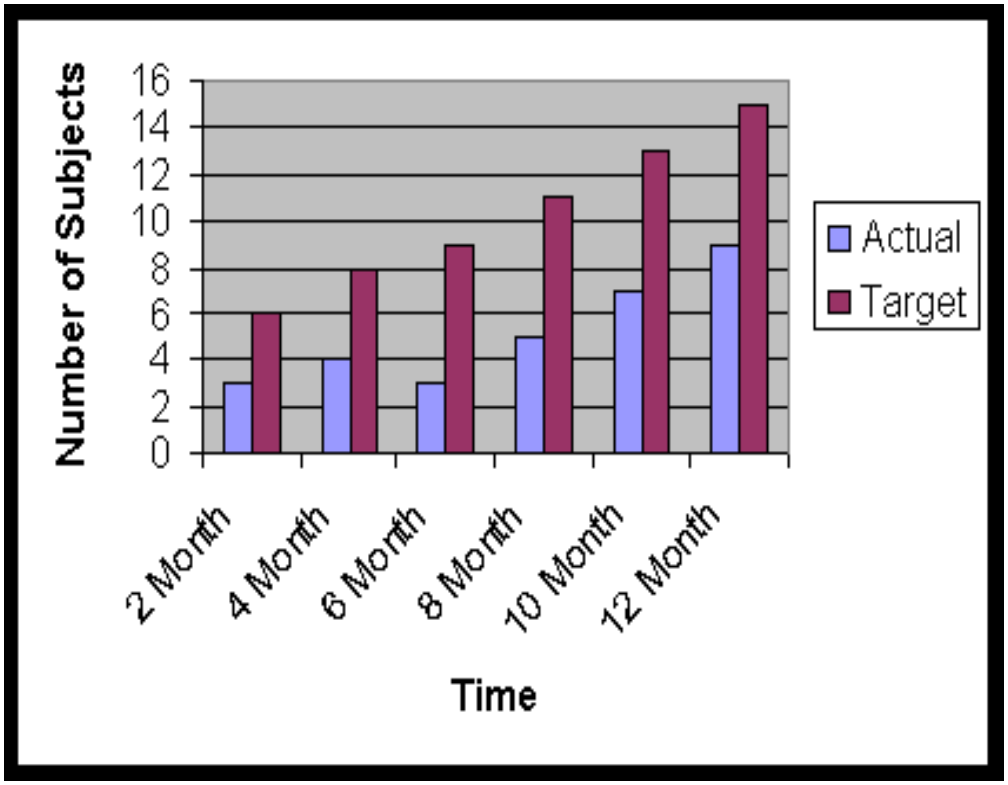


Figure 2. COMPARISON OF TARGET TO ACTUAL ENROLLMENT BY SITE

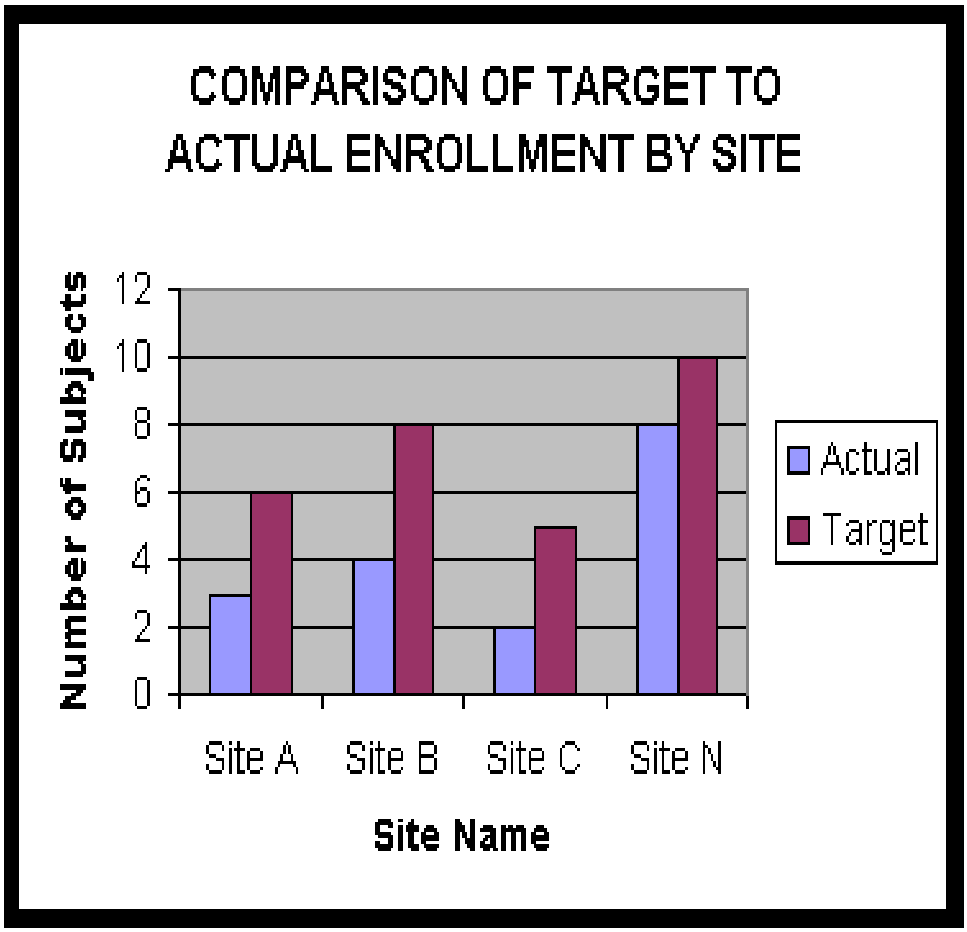


Table 2. OVERALL SUBJECT STATUS BY SITE

Date: _____

Site Number and Name	Screened	Date Enrolled	Date Completed	Active	Terminated/Dropped Out (reason)
1					
2					
3					
4					
N					
Total					

TABLE 3.
SUBJECT STATUS-DETAIL BY SITE

Date: _____

Drug Permanently Discontinued

Site	Total Enrolled	Active	Completed	Concurrent Illness	Patient Consent Withdrawn	Adverse Event	Patient Stops Medication	Other
1								
2								
3								
4								
N Total								

***Note: It may be important to further capture information about patient withdrawal. Some suggested categories might be:**

1) Permanent drug discontinuation (serious adverse event), patient continues follow up
2) Permanent drug discontinuation (serious adverse event), patient refuses follow up
3) Patient stops drug (a specific reason e.g. side effects, inconvenience), patient continues follow up
4) Patient stops drug (a specific reason e.g. moves, side effects), but refuses further follow up
5) Patient lost to follow up (no explanation given)

Table 4. DATA FLOW TO COORDINATING CENTER
BY VISIT AND SITE

Date: _____

Site Number and Name	Screening/Baseline Expected N	Screening/Baseline Received N	Study Completion N%	Follow-Up N%
1				
2				
3				
4				
N				
Total				

Table 5. STATUS OF FORMS AT COORDINATING CENTER

Date: _____

	Baseline	Follow-up	Completed	Total
1. Number of Subjects in Study Database	**N**	**N**	**N**	**N**
2. Number of Forms Entered	**N**	**N**	**N**	**N**
3. Total Number of Subjects Forms Double-Entered	**N**	**N**	**N**	**N**
4. Total Number of Forms Edited	**N(%)**	**N(%)**	**N(%)**	**N(%)**
5. Total Number of Forms Completed	**N(%)**	**N(%)**	**N(%)**	**N(%)**

Table 6. RACE/ETHNIC CHARACTERISTICS FOR ALL SUBJECTS

Date: _____

TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date by Ethnicity and Race				
Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino				
Not Hispanic or Latino				
Unknown				
Ethnic Category: Total of All Subjects				
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian /Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or unreported				
Racial Categories: Total All Subjects				
HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date				
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian/Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or unreported				
Racial Categories: Total All Subjects				

Table 7. RACE/ETHNIC CHARACTERISTICS BY SITE

Date: _____

	Hispanic/Latino										Not Hispanic/Latino											
Site# and/or Name	American Indian/ Alaska Native		Asian Pacific		Native Hawaiian or Other Pacific Islander		Black or African American		White		American Indian/ Alaska Native		Asian Pacific		Native Hawaiian or Other Pacific Islander		Black or African American		White		**Total**	
	M	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***	***M***	***F***

Table 8. DEMOGRAPHIC AND KEY BASELINE CHARACTERISTICS BY GROUP

Date: _____

Characteristics	Group 1 N%	Group 2 N%	Total N%
Gender			
- Male			
- Female			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			
Race			
- American Indian/Alaska Native			
- Asian			
- Native Hawaiian or Other Pacific Islander			
- Black or African American			
- White			
- More than one race			
- Unknown or not reported			
Age			
- Mean			
- Median			
- Minimum			
- Maximum			
Risk Factors			
Clinical Features			

Table 9. TREATMENT DURATION FOR ALL SUBJECTS

Date: _____

Time in Study	A		B		Total
	N	%	N	%	
1 Month or less					
2-5 Months					
6-9 Months					
10-11 Months					
Completed Study					

Table 10. TREATMENT DURATION FOR SUBJECTS WHO DISCONTINUE THERAPY

Date: _____

Time in Study	A		B		Total
	N	%	N	%	
1 Month or less					
2-5 Months					
6-9 Months					
10-11 Months					
Completed Study					

Table 11. ADVERSE EVENTS BY SITE AND SUBJECT

Date: _____

Site:_____

[A separate table can made for each site]

***= See Codes**

Subject	Adverse Event	Onset Date	Ending Date	*Severity	*Drug Related	*Action	*Outcome	Comments

CODES:

Severity:
1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening**

Drug Relatedness:
0 = Definitely unrelated
1 = Unlikely
2 = Possibly Related
3 = Probably Related
4 = Definitely Related

Action (taken):
0 = None
1 = Dose modification
2 = Counteractive Medication (specify under comments)
3 = Medical/surgical intervention (specify under comments)
4 = Hospitalization**
5 = Drug permanently discontinued
6 = Other (specify under comments)

Outcome:
1 = Resolved
2 = Recovered with minor sequelae
3 = Recovered with major sequelae
4 = Condition still present and under treatment
5 = Condition continues to worsen
6 = Patient died**

****Event is serious and explained in detail on SAE form**

Table 12. SERIOUS ADVERSE EVENTS BY SITE AND SUBJECT

Date: _____

Site:_____

[A separate table can made for each site]

Subject	Age	Treatment Date	Event	Onset Date	*Relationship	Description of Actions and Outcome (e.g., hospitalization concomitant meds, study, status, etc.)

<u>*RELATIONSHIP</u>
0 = Definitely Unrelated
1 = Unlikely
2 = Possibly Related
3 = Probably Related
4 = Definitely Related

<u>NOTE:</u> Whether or not the event is "expected" might also be included in this table. "Expected" means the event is part of the natural course of the disease process or the event is a known consequence of the treatment as identified in the protocol or the investigator's brochure. This may be important information if this study is using an investigational or IND drug.

Table 13. DEATHS BY SITE

Date: _____

Site # and Name	Patient ID#	DOB	Date Enrolled	Treatment Duration	Cause of Death	Date of Death
1						
2						
3						
4						
N						

Table 14. FREQUENCY OF SPECIFIC SYMPTOMS

Date: _____

Symptoms (depends on disease)	N%
Pain or Heaviness in Legs	
Swelling in Legs	
Pain or Heaviness in Chest	
Headaches	
Dizziness	
Nausea	
Abdominal Pain	
Weakness	
Fatigue	
Muscle Aches	
Urinary Frequency	
Total	

Table 15. OBSERVED ADVERSE EVENTS BY BODY SYSTEM

Date: _____

ADVERSE EVENT	SEVERITY		RELATIONSHIP TO DRUG			
	Mild/Mod	Severe	Related Drug A Only	Related to Drug B Only	Related to Both	Not Related
Body System A:						
Event 1						
Body System B:						
Event 1						
Body System C:						
Event 1						

Table 16. LABORATORY DATA BY PATIENT:
OUT OF RANGE VALUES

Date: _____

Pt. ID#	Visit #	HCT	WBC	PLT	Protein	Urine RBC	Creatinine	ALT	AST	Cholesterol	Amylase	BUN	CPK

Table 17. SUBJECT STATUS BY SITE AND GROUP

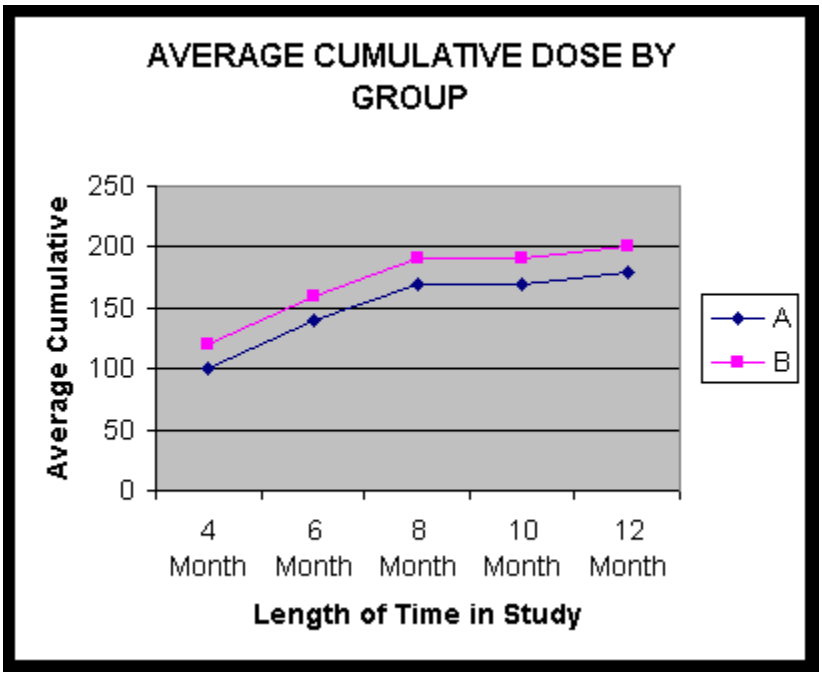
Date: _____

Terminated

				Concurrent Illness		Withdrawal of Consent		Adverse Event		Lost to Follow-Up		Other	
Site # and Name	Total Enrolled	Active	Completed	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
1													
2													
3													
4													
N													

Figure 3. AVERAGE CUMULATIVE DOSE BY GROUP

Date: _____



APPENDIX B: Sample DSMB Charter

DSMB Charter
[Title of Study]
***[PI name]*, Principal Investigator**
[Grantee Institution]

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to NIDDK to monitor patient safety and evaluate the efficacy of the intervention. Dr. [PI name], University of [*where], [location]* is conducting a clinical trial entitled, "[*title of study]*" under a [*grant or cooperative agreement or contract*] with the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK).

DSMB RESPONSIBILITIES

The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval, and at periodic intervals (to be determined) during the course of the trial, the DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the NIDDK, the PI, and, if required, to the Food and Drug Administration (FDA) and the Institutional Review Board (IRB) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;

- if appropriate, conduct interim analysis of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB;

- ensure the confidentiality of the trial data and the results of monitoring; and,

- assist NIDDK by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

MEMBERSHIP

The DSMB will consist of at least five members. Three members will constitute a quorum. The members have been recommended by Dr. *[PI];* the NIDDK has approved the composition of the DSMB, and appointed the members. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Collaborators or associates of Dr. *[PI]* are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required. The DSMB includes experts in or representatives of the fields of:

- relevant clinical expertise,
- clinical trial methodology, and
- biostatistics.

Dr. [*who]*, University of *[...]*, has been selected by NIDDK in consultation with the PI to serve as the Chairperson. He is responsible for overseeing the meetings, developing the agenda in consultation with the NIDDK Program Official and the PI. The chair is the contact person for the DSMB. The NIDDK Official, *[name of NIDDK Official]* will serve as the Executive Secretary (ES) for the DSMB. The *[Grantee Institution]* shall provide the logistical management and support of the DSMB.

A Safety Officer will be identified by the PI at the first meeting. This person will be the contact person for severe adverse event reporting. Procedures for notifying the Chair of the DSMB and the NIDDK Program Official will be discussed at the first meeting.

BOARD PROCESS

The first meeting will take place face-to-face to discuss the protocol, any modifications of the trial, and to establish guidelines to monitor the study. The NIDDK Program Official, the DSMB Chairperson and the PI will prepare the agenda to address the review of manual of operating procedures, modification of the study design, initiation of the trial, identification of a safety officer, reporting of adverse events, stopping rules, interim analysis plan, etc.

Meetings of the DSMB will be held two times a year at the call of the Chairperson, with advance approval of the NIDDK Program Official. A NIDDK Official(s) will be present at every meeting.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff. Meetings may be convened as conference calls as well as in person, although the initial meeting and meetings to discuss interim analysis will be face-to-face. An emergency meeting of the DSMB may be called at any time by the Chairperson or by NIDDK should questions of patient safety arise.

MEETING FORMAT

An appropriate format for DSMB meetings consists of an open and a closed session. The open sessions may be attended by the principal investigator(s), institution staff and NIDDK staff, but should always include the study biostatistician. Issues discussed at open sessions will include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session will be attended only by voting DSMB members and the NIDDK ES. The DSMB may request others to attend by part or all of the closed session (e.g., study statistician, NIDDK staff). All safety and efficacy data are and must be presented at this session. The discussion at the closed session is completely confidential.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended.

REPORTS

1. **Interim Reports:** Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB at least 10 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

   Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status.

   Part 2 (Closed Session Report) may contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential and should be destroyed at the

conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping is clearly defined.

2. Reports from the DSMB: A formal report containing the recommendations for continuation or modifications of the study prepared by the ES with concurrence from the DSMB Chairperson will be sent to the full DSMB within 4 weeks of the meeting. Once approved by the DSMB, the NIDDK will forward the formal DSMB recommendation report to the PI. It is the responsibility of the PI to distribute the formal DSMB recommendation report to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

As previously stated, the formal DSMB report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The NIDDK is responsible for notifying the PI of a decision to terminate the study. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members or to the designated safety officer (to be determined at the first meeting). Any concerns noted should be brought to the attention of the DSMB Chairperson or designated safety officer and the NIDDK Program Official.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

APPENDIX C: Sample Conflict of Interest Form

CONFIDENTIAL

CONFLICT OF INTEREST STATEMENT FOR DSMB MEMBERS

"[Title of Study]"
***[Principal Investigator name]*, Principal Investigator**
[Grantee Institution]

As noted below:

- I am not a part-time, full-time, paid, or unpaid employee of any organizations that are: (a) involved in the study under review; (b) whose products will be used or tested in the study under review, or whose products or services would be directly and predictably affected in a major way by the outcome of the study;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations.

- I do not have any financial interests or assets in any organizations meeting the above criteria, not does my spouse, dependent children, nor any organization with which I am connected; and

- I am not a current collaborator or associate of the principal investigator.

Having read the above: *(please check the appropriate answer)*
___ I have no relevant interests or activities.
___ I have noted any exceptions in the space below:

I will notify the NIDDK promptly if:

- a change occurs in any of the above during the tenure of my responsibilities, or

- I discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

	_____	_____
[Board Member]	Signature	Date
[Name]	_____	_____
NIDDK Official	Signature	Date